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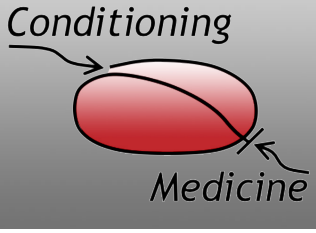

REVIEW ARTICLE | OPEN ACCESS

Ameliorative potential of conditioning on ischemia-reperfusion injury in diabetes

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[Received: 23 March 2018; accepted: 11 April 2018; published online 20 April, 2018]

Diabetes is a serious metabolic disease characterized by hyperglycemia. Diabetes also leads to several long-term secondary complications. Cardiovascular disease is an important complication of diabetes and is a major contributor to morbidity and mortality in diabetic subjects. The discovery of conditioning-induced ischemic or anoxic tolerance has led to the demonstration of the protective potential of conditioning as a treatment strategy to mitigate ischemia-reperfusion injury. Diabetes modulates multiple metabolic pathways and signal transduction cascades. Some of these pathways may overlap with mechanisms that mediate the beneficial effects of conditioning from the body's reaction to a sublethal insult, indicating the possibility of a potential interaction between diabetes and conditioning. Studies demonstrate that diabetes abrogates the ameliorative effect of various forms of conditioning, such as ischemic preconditioning, ischemic postconditioning, remote ischemic conditioning and pharmacological conditioning, on ischemia-reperfusion injury in various animal models. Moreover, drugs used to treat diabetes may have a potential impact on protection afforded by conditioning from ischemic injury. Potential impact of various anti-diabetic drugs on conditioning-induced protection is also discussed. Overall, the literature suggests that a better understanding of the overlap among pathways activated by diabetes and those involved in induction of ischemia tolerance may help identify ideal conditioning paradigms to protect diabetic subjects from ischemic injury.

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The American Diabetes Association defines diabetes mellitus as a "a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both" (American Diabetes Association, 2014). Approximately 30.3 million Americans are suffering from diabetes, and the economic burden due to diabetes was $320 billion in 2015 (Centers for Disease Control and Prevention, 2017). Chronic diabetes produces long-term detrimental changes in several organs leading to development of cardiovascular diseases, neuropathy, retinopathy and nephropathy, among other secondary complications (Bhalla et al., 2013; American Diabetes Association, 2014; de Ferranti et al., 2014; Kolber and Scrimshaw, 2014; Fox CS, 2015; National Eye Institute, 2015; Afkarian et al., 2016; Huo X, 2016; Tracey et al., 2016; Pop-Busui et al., 2017; American Optometric Association, 2018). Diabetes also increases the prevalence of and mortality resulting from brain ischemia and myocardial injury (Centers for Disease Control and Prevention, 2003; Almdal et al., 2004; Ottenbacher et al., 2004; Kissela et al., 2005; Alegria et al., 2007; Marso et al., 2007).

Diabetes and ischemia-reperfusion injury

Diabetes is an established risk factor for ischemic stroke and coronary heart disease (Schramm et al., 2008; Spencer et al., 2008). A meta-analysis of 102 prospective studies demonstrated that diabetes causes about a two-fold increase in the risk of ischemic stroke, coronary heart disease, and deaths ascribed to other vascular complications (Emerging Risk Factors Collaboration et al., 2010). Both type 1 diabetes (T1D) and type 2 diabetes (T2D) enhance cardiovascular mortality and morbidity (Fuller et al., 2001; Janghorbani et al., 2007). The pathophysiology of increased progression and risk of cardiovascular diseases in diabetes patients is not well understood. Pronounced increase in risk factors such as dyslipidemia, hypercoagulability, endothelial dysfunction, and inflammation in diabetic patients may increase the risk of cardiovascular diseases (Plutzky and Brown, 2012). This role has been established by several groups (see reviews (Fonseca et al., 2004; Martin-Timon et al., 2014; Leon and Maddox, 2015)). In comparison to non-diabetic subjects, diabetic individuals display enhanced lipid-rich atheroma, macrophage infiltration and formation of thrombus in the coronary arteries (Moreno et al., 2000). Atherosclerotic plaques in diabetic patients have higher levels of macrophages, T lymphocytes, and inflammatory cells (human leukocyte antigen–DR positive cells) (Cipollone et al., 2003). Accelerated atherosclerosis is seen in diabetic individuals (Otsuka et al, 2012). Overall, the above factors lead to increased risk of thrombosis and subsequent tissue ischemia in diabetics. Therefore, there is a need to develop novel therapeutic approaches to mitigate ischemic injury in diabetic subjects. Research efforts worldwide have focused on evaluating numerous potential strategies to salvage tissue from ischemic damage. The discovery of ischemic/pharmacologic preconditioning, postconditioning and remote conditioning has uncovered novel ways to activate multiple cytoprotective signaling pathways to confer protection against ischemic injury (Dave et al., 2001; Dave et al., 2006; Raval et al., 2006a; Raval et al., 2006b; Koronowski et al., 2015; Hausenloy et al., 2016). The goal of this review article is to describe the published literature that has evaluated the efficacy of conditioning in lowering ischemia-reperfusion injury in the diabetic condition.

Conditioning

Conditioning denotes the "adaptive process of endogenous protection in which small doses of sub-lethal ischemia protects the organism against a lethal ischemic event" (Adstamongkonkul, 2017). The term *conditioning* is broadly used to describe the induction of ischemia tolerance by a group of various paradigms. These paradigms include ischemic preconditioning, perconditioning, postconditioning, remote conditioning and pharmacological conditioning. The term ischemic preconditioning describes the protective effect induced by episode(s) of brief ischemia, too brief in themselves to cause tissue damage, before an episode of severe ischemia (Przyklenk, 2013). Ischemic preconditioning is a promising approach to lower the extent of ischemic injury in the heart (Murry et al., 1986), brain (Kitagawa et al., 1990), kidney (Lee and Emala, 2000), small intestine (Pajdo et al., 2001), skeletal muscle (Mounsey et al., 1992) and liver (Lloris-Carsi et al., 1993). Various types of stress conditions such as cortical spreading depression (Kobayashi et al., 1995), electroacupuncture (Xiong et al., 2003), mild epileptic insult (Plamondon et al., 1999), thrombin (Masada et al., 2000), hyperbaric oxygen preconditioning (Wada et al., 1996), and exercise (Lennon et al., 2004; Quindry et al., 2005; McGinnis et al., 2015) also induce ischemia tolerance in various organs. Ischemic perconditioning refers to a therapeutic strategy designed to reduce infarct size by application of conditioning stimulus during the ischemic event (Vinten-Johansen and Shi, 2011). Ischemic postconditioning induces tolerance by restoring blood flow to the ischemic tissue in an intermittent manner, before complete reperfusion occurs (after the severe ischemic insult). This type of conditioning is shown to protect heart (Zhao et al., 2003), brain (Zhao et al., 2006), liver (Sun et al., 2004), kidney (Jonker et al., 2016), and intestines (Sengul et al., 2013; Jia et al., 2017) from ischemia-reperfusion injury. In the case of both ischemic preconditioning and postconditioning, the site exposed to the protective stimulus (brief episodes of ischemia or modified reperfusion) as well as severe ischemia are typically the same. However, in the case of remote ischemic conditioning, brief episode(s) of ischemia on a tissue or organ exert a protective effect on a distant tissue or organ subjected to ischemia (Przyklenk et al., 1993; Dave et al., 2006). Remote conditioning includes remote preconditioning, perconditioning and postconditioning when the remote ischemic event is elicited before, during and after the major ischemic event, respectively. Mechanistic understanding of various forms of conditioning have implicated the possibility of artificially (without inducing ischemia) activating mechanisms mediating ischemic conditioning. This type of conditioning is referred to as pharmacological conditioning (Julier et al., 2003; Luca et al., 2011). Below we provide a summary of literature that has used various conditioning paradigms to protect tissues and organs against ischemic injury in animal models of diabetes (Table 1).

Ischemic preconditioning and protection in diabetes

Ischemic preconditioning is a paradigm that induces protection against ischemic damage in the same tissue or organ (Murry et al., 1986; Kitagawa et al., 1990; Mounsey et al., 1992; Lloris-Carsi et al., 1993; Stagliano et al., 1999; Lee and Emala, 2000; Pajdo et al., 2001; Dave et al., 2005). As mentioned above, an increase in the risk factors for cardiovascular disease in diabetes enhances the risk of ischemia and the extent of ischemic damage. Therefore, to understand the potential therapeutic benefit of preconditioning during diabetes, studies have evaluated the effect of preconditioning in animal models of diabetes. Ischemic preconditioning of kidney (four cycles of 4-min ischemia followed by 11-min reperfusion) did not produce any ameliorative effect on ischemia-reperfusion-induced injury in streptozotocin diabetic rats (diabetes was induced 1 month prior to ischemia) when histological and biochemical markers were used as surrogates for tissue damage (Ozbilgin et al., 2016). A group using a canine model demonstrated that diabetic and acutely hyperglycemic animals display a reduced protective effect of ischemic preconditioning on coronary artery occlusion/reperfusion-induced myocardial infarction (Kersten et al., 1998; Kersten et al., 2000). Ischemic

Table 1: Summary of studies on the effect of diabetes on conditioning.

Type of Conditioning	Diabetic/ Non-diabetic Population	Model of Ischemia	Conditioning Stimulus	Induction of Protection	Reference(s)
Preconditioning	T1D rats	Kidney ischemia *in vivo*	4 x 4 min ischemia	No	Ozbilgin et al., 2016
	T1D/Hyperglycemic dogs	Myocardial ischemia *in vivo*	4 x 5 min ischemia	No	Kersten et al., 1998, 2000
	T1D sheep	Myocardial ischemia *in vivo*	6 x 5 min ischemia	No	del Valle et al., 2003
	Zucker obese rats	Myocardial ischemia *in vivo*	6 x 5 min ischemia	No	Katakam et al., 2007
	T1D rats	Isolated heart preparation	4 x 5 min ischemia	No	Tosaki et al., 1996
	T1D/Hyperglycemic rabbits	Myocardial ischemia *in vivo*	1 x 5 min ischemia	No	Ebel et al., 2003
	T1D rats	Isolated heart preparation	1 x 5 min ischemia	No	Bouchard and Lamontagne, 1998
	T2D rats	Isolated heart preparation	4 x 1 min ischemia	No	Kristiansen et al., 2004
	T2D rats	Isolated heart preparation	3 x 5 min ischemia	No	Tsang et al., 2005
	T2D rats	Isolated heart preparation	1 or 3 x 5 min ischemia	No	Hausenloy et al., 2013
	T1D rats	Focal cerebral ischemia-induced brain injury	3 x 10 min ischemia	Yes	Altintas et al., 2016a; 2016b
	Non-diabetic	Organotypic cultures of the hippocampus	Hypoxia/hypoglycemia	Yes	Badaut et al., 2005
	T1D rats	Retinal ischemia	5-min ischemia, weekly repetitions	Yes	Fernandez et al., 2011, 2012
	T1D rats	Intestine and liver ischemia	1 x 10 min ischemia	Yes	Thomaz Neto et al., 2013
Postconditioning	T1D and T2D mice	Isolated heart preparation	3 or 6 x 10 sec ischemia	No	Przyklenk et al., 2011
	T1D rats	Myocardial ischemia *in vivo*	3 x 20 sec ischemia	No	Drenger et al., 2011
	T2D mice	Myocardial ischemia *in vivo*	6 x 10 sec ischemia	No	Bouhidel et al., 2008; Zhu et al., 2012
Remote Preconditioning	T1D rats	Myocardial ischemia *in vivo*	4 x 5 min liver ischemia	No	Hu et al., 2017
	Hyperglycemia	Myocardial ischemia *in vivo*	3 x 5 min femoral artery and vein occlusion	No	Baranyai et al., 2015
	T1D	Myocardial ischemia *in vivo*	1 x 15 min femoral artery occlusion	No	Kiss et al., 2014
	Diabetic human subjects	Myocardial infarction	Intermittent upper arm ischemia	No	Moretti et al., 2018
Pharmacological Preconditioning	Hyperglycemia in rabbits	Myocardial ischemia *in vivo*	Isoflurane postconditioning	No	Raphael et al., 2010
	Hyperglycemia in dogs	Myocardial ischemia *in vivo*	Isoflurane preconditioning	No	Kehl et al., 2002
	T1D dogs	Myocardial ischemia *in vivo*	Isoflurane preconditioning	No	Tanaka et al., 2002
	T1D rats	Myocardial ischemia *in vivo*	Sevoflurane postconditioning	No	Drenger et al., 2011; Tai et al., 2012
	T1D rats	Myocardial ischemia *in vivo*	Erythropoietin postconditioning	No	Ghaboura et al., 2011
	T1D rats	Myocardial ischemia *in vivo*	Morphine preconditioning	No	Gross et al., 2007
	T2D rats	Myocardial ischemia *in vivo*	Erythropoietin and [D-Ala2, D-Leu5]-enkephalin acetate - preconditioning	No	Hotta et al., 2010
	T2D rats	Myocardial ischemia *in vivo*	Isoflurane-induced preconditioning	No	Matsumoto et al., 2009

T1D: Type 1 diabetes; T2D: Type 2 diabetes.

preconditioning produced by six cycles of 5-min ischemia and a 5-min reperfusion period did not exert any ameliorative effect on stunning in ischemic heart in diabetic sheep when evaluated in both the first and second window of preconditioning. Instead, the first window of preconditioning worsened ischemia-reperfusion-induced myocardial damage as measured in terms of mechanical function (del Valle et al., 2003). While ischemic preconditioning elicited by a cycle of 5 min of ischemia and 5 min of reperfusion decreases infarct size in the myocardium exposed to 30 mins of left coronary artery ligation and 4 hours of reperfusion in heart of Zucker lean rats, this protection is abolished in insulin-resistant Zucker obese rats (Katakam et al., 2007). In addition, long-term diabetes (4 and 8 weeks of streptozotocin-induced diabetes) is also associated with the lack of protective effect of ischemic preconditioning on ventricular fibrillation, tachycardia, cardiac function, and ion shift abnormalities induced by 30-min ischemia / 30-min reperfusion (Tosaki et al., 1996). In an *in vivo* rabbit model of myocardial ischemia, acute hyperglycemia and diabetes attenuated the cardioprotective effect of the second window of ischemic preconditioning (5 min of left descending coronary artery occlusion) against myocardial ischemia (30 min of ischemia and 2 h of reperfusion) when damage was evaluated in terms of the myocardial infarct size (Ebel et al., 2003). Moreover, diabetic inhibition of myocardial preconditioning was refractory to acute insulin treatment (Ebel et al., 2003). This study suggests that simple correction of hyperglycemia is not able to restore the protective effects of ischemic preconditioning.

Ischemic preconditioning with a single episode of ischemic insult involving 5-min ischemia and 10-min reperfusion prevents ischemia-reperfusion-induced endothelial dysfunction in non-diabetic hearts but not in diabetic hearts (Bouchard and Lamontagne, 1998). However, three such episodes of preconditioning produced a similar beneficial effect on the diabetic heart (Bouchard and Lamontagne, 1998). This study suggests that a more extensive preconditioning stimulus is required to condition diabetic hearts. Ischemic preconditioning induced by 4 cycles of 2 min of ischemia and 3 min of reperfusion does not exert any significant effect on the extent of myocardial infarction induced by 50 min of ischemia and 120 min of reperfusion in rat hearts isolated from Zucker diabetic fatty (obese model of T2D) and lean Goto-Kakizaki rats (lean model of T2D) (Kristiansen et al., 2004). Experiments on isolated rat heart preparation observed that while a single short (5-min) episode of ischemic preconditioning elicits a protective effect only on non-diabetic heart, more severe ischemic preconditioning stimuli involving three episodes of 5-min ischemia are required to produce a similar effect on heart of Goto-Kakizaki rats (Tsang et al., 2005). This study also demonstrated that the ischemic preconditioning stimuli should be strong enough to increase the Akt phosphorylation necessary to achieve threshold for cardioprotection. Based on this observation, in a follow-up study this group of investigators evaluated the effect of glimepiride -- a known activator of Akt. They observed that glimepiride treatment was able to lower the threshold for ischemic preconditioning in such a manner that both 1 and 3 cycles of ischemic preconditioning involving cycle(s) of 5 minutes of global ischemia and 10 minutes of reperfusion produced a cardioprotective effect in diabetic heart isolated from Goto-Kakizaki rats (Hausenloy et al., 2013). This indicates that while a higher intensity of preconditioning stimuli is required to observe protective effects on ischemic myocardium, the treatment with glimepiride, an anti-diabetic drug, lowers the threshold of preconditioning stimuli required to observe the protective effect of ischemic preconditioning on diabetic heart. This study also demonstrates that glimepiride reverses the effect of diabetes on ischemic preconditioning, possibly due to its interaction with the pathways mediating the beneficial effect of ischemic preconditioning on myocardium. However, further studies with other drugs that activate conditioning pathways are required to further confirm this premise.

A limited number of studies have evaluated mechanisms involved in suppression of conditioning-induced ischemia tolerance in diabetic animals. The inhibitory effect of diabetes on myocardial preconditioning is implicated by dysfunction in sarcolemmal K_{ATP} channels (del Valle et al., 2003). Dysfunction of mitochondrial K_{ATP} channels is also proposed to mediate diabetic attenuation of the protective effect of myocardial preconditioning (Ghosh et al., 2001). Glycogen synthase kinase-3β also mediated diabetic attenuation of the beneficial effect of ischemic preconditioning (4 cycles of 5-min ischemia and 5-min reperfusion) on the isolated rat heart exposed to ischemia-reperfusion injury (Yadav et al., 2010). However, better understanding of conditioning mechanisms affected in diabetes may help design novel strategies to induce ischemia tolerance in diabetics.

The effect of ischemic preconditioning has also been evaluated in other tissues and organs in diabetes. Ischemic preconditioning 72 h prior to ischemia exerts a significant ameliorative effect on transient focal cerebral ischemia-induced brain injury in both non-diabetic and diabetic rats (seven days post-streptozotocin injection) with a concomitant upregulation of pro-survival miRNAs in the infarcted brain area (Altintas et al., 2016a; Altintas et al., 2016b). It is possible that longer (several weeks) and not short duration (7 days) of diabetes may attenuate the protective effect of ischemic preconditioning. Hypoxia/hypoglycemia-induced preconditioning decreases delayed ischemic cell death and the extent of loss of functional electrical activity in organotypic slice cultures (Badaut et al., 2005). Previously, our laboratory showed that prior exposure to recurrent hypoglycemia enhances ischemic brain injury in insulin-treated diabetic rats (Dave et al., 2011b) and oxygen glucose deprivation-induced damage in hippocampal organotypic slices (Dave et al., 2011a). Ischemic conditioning induced by weekly repetitions of 5 min of retinal ischemia in streptozotocin diabetic rats prevented axoglial changes in the optic pathway. These axoglial changes include deficits in the anterograde transport from the retina to the superior colliculus, increase in astrocyte reactivity, ultrastructural alteration in myelin, and altered oligodendrocyte morphology in the distal portion of the optic nerve (Fernandez et al., 2011; Fernandez et al., 2012). These studies again emphasize that stronger preconditioning stimuli (weekly repetitions of conditioning stimuli) may be needed to induce ischemia tolerance in diabetic eyes of diabetic individuals. Ischemic preconditioning of intestine and liver of diabetic rats prior to severe ischemia in the respective organs reduced leukocyte infiltration in the lungs (Thomaz Neto et al., 2013). In summary, a longer duration of diabetes may attenuate the protective effects of ischemic preconditioning, and stronger conditioning stimuli may be required to induce ischemia tolerance in diabetic animals. However, further detailed studies are required to understand the effect of chronic diabetes on ischemia-reperfusion injury in brain, kidney, intestines and liver.

Ischemic postconditioning and protection in diabetes

Ischemic postconditioning exerts a potent protective effect on tissues or organs subjected to otherwise severe ischemic insult (Zhao et al., 2003; Kin et al., 2004; Kin et al., 2005; Zhao et al., 2006). Details appear in earlier reviews (Zhao, 2007, 2009; Zhao et al., 2012; Theodoraki et al., 2016). Clinical studies also confirmed the beneficial effects of ischemic postconditioning on ischemic myocardium (Staat et al., 2005; Hansen et al., 2010). However, ischemic postconditioning induced by three or six 10-s cycles of reperfusion-reocclusion on an isolated mouse

heart preparation did not produce any beneficial effect on the extent of infarct size in the *db/db* mouse model of T2D and streptozotocin-induced mouse model of T1D (Przyklenk et al., 2011). Four to five weeks of streptozotocin-induced diabetes attenuates the ameliorative effect of ischemic postconditioning on ischemia-reperfusion injury-induced myocardial infarction in rats *in vivo* (Drenger et al., 2011). Similarly, the ischemic postconditioning-induced reduction in myocardial infarct size (observed in control mice) was not observed in *db/db* mice and leptin-deficient obese (*ob/ob*) mice subjected to myocardial ischemia (Bouhidel et al., 2008; Zhu et al., 2012). These studies indicate that ischemic postconditioning does not confer beneficial effects on ischemia myocardium in multiple models of diabetes. The effect of ischemic postconditioning on other ischemic tissues and organs in diabetic animals remains to be established.

Remote ischemic conditioning and protection in diabetes

Preclinical data demonstrates that remote ischemic conditioning (RIC) can induce protection against ischemic damage (Hausenloy and Yellon, 2008; Heusch et al., 2015; Pickard et al., 2015; Sivaraman et al., 2015; Giannopoulos et al., 2017). Remote ischemic preconditioning elicited by transient liver ischemia reduces the incidence of ventricular tachyarrhythmias in both non-diabetic and diabetic rats. However, in comparison to non-diabetic rats, remote preconditioning failed to exert a beneficial effect on atrioventricular block in diabetic rats (Hu et al., 2017).

Acute hyperglycemia attenuates the cardioprotective effect of remote femoral artery and vein occlusion-induced remote perconditioning on ischemic myocardium (induced by transient occlusion of the left anterior descending coronary artery for 40 min) *in vivo* (Baranyai et al., 2015). This study demonstrated that remote perconditioning in acute hyperglycemic rats did not influence infarct size but increased incidence as well as duration of arrhythmias. They also hypothesized that deterioration in cardioprotection by remote preconditioning in acute hyperglycemic rats may be due to increased nitrative stress. Remote ischemic perconditioning induced by bilateral femoral artery occlusion exerts a significant protective effect on left coronary artery occlusion-induced myocardial ischemia and associated infarct size in nondiabetic rats. However, this protective effect was absent in diabetic rats (Kiss et al., 2014).

A recent double blinded, randomized, placebo-controlled, multicenter clinical study demonstrated that remote ischemic preconditioning induced by four cycles of intermittent upper arm ischemia–reperfusion exerts a protective effect on contrast-induced nephropathy in non-diabetic subjects with moderate renal dysfunction undergoing percutaneous coronary intervention (Moretti et al., 2018). However, they did not observe a similar protective effect of remote ischemic preconditioning (RIC) on diabetic patients (Moretti et al., 2018). Clinical studies evaluating the efficacy of RIC on the ischemic myocardium (in terms of levels of marker of ischemic cell death) showed either beneficial (Cheung et al., 2006; Hausenloy et al., 2007; Ali et al., 2010; Kottenberg et al., 2012; Candilio et al., 2015) or no effect (Gunaydin et al., 2000; Karuppasamy et al., 2011; Lucchinetti et al., 2012; McCrindle et al., 2014). It is plausible that such a mixed result may be due to patient populations with various comorbidities such as diabetes. Overall, studies evaluating the effect of diabetes on remote conditioning are minimal, and more studies are required to understand the effect of diabetes on the protective effect of remote ischemic preconditioning.

Pharmacological conditioning and protection in diabetes

Activating ischemia tolerance pathways via pharmacological conditioning exerts a protective effect against ischemic damage (Julier et al., 2003; Luca et al., 2011; Wang et al., 2011; Shi et al., 2013). However, the effect of pharmacological conditioning on ischemic damage in diabetic animals or human subjects is not well understood. Acute hyperglycemia attenuates isoflurane postconditioning-induced reduction in myocardial infarct size and creatine kinase levels in a rabbit heart ischemia-reperfusion model (Raphael et al., 2010). In addition, moderate to severe hyperglycemia prevented the cardioprotective effect of isoflurane preconditioning on dogs subjected to left anterior descending coronary artery occlusion-reperfusion-induced injury (Kehl et al., 2002). The effect of isoflurane-induced preconditioning of the myocardium is also attenuated in alloxan- and streptozotocin-treated dogs (Tanaka et al., 2002). Sevoflurane postconditioning-induced cardioprotection is lost in streptozotocin-diabetic rats (Drenger et al., 2011; Tai et al., 2012). Erythropoietin postconditioning-induced reduction in myocardial infarct size was observed in a cohort of rats with high-fat diet-induced insulin resistance syndrome. However, the protection was abrogated in streptozotocin-induced diabetic rats (Ghaboura et al., 2011). This study also concluded that disruption of glycogen synthase kinase-3beta (GSK-3β) signaling may be responsible for observed abolished erythropoietin-induced cardioprotection in streptozotocin-induced diabetic rats. The cardioprotective effect of erythropoietin and [D-Ala2, D-Leu5]-enkephalin acetate (a delta-opioid receptor agonist) preconditioning was abolished in a rat model of T2D (Otsuka-Long-Evans-Tokushima fatty rats) (Hotta et al., 2010). However, blockade of angiotensin II type 1 receptor for a period of 2 weeks restored the cardioprotective effect of erythropoietin preconditioning in diabetic animals (Hotta et al., 2010). Similarly, morphine preconditioning did not affect ischemia-reperfusion-induced infarct size in streptozotocin-diabetic rats, but reduced infarct size in the nondiabetic group (Gross et al., 2007). This study also concluded that this abolished morphine-induced cardioprotection in diabetic rats was due to reduced activation of mediators of GSK-3β signaling. While isoflurane-induced preconditioning of heart produced a beneficial effect in non-diabetic Wistar rats, it failed to exert a similar effect on Goto-Kakizaki rats (Matsumoto et al., 2009). However, olprinone preconditioning protected hearts of Goto-Kakizaki rats against myocardial infarction potentially via the phosphatidylinositol 3-kinase-Akt pathway (Matsumoto et al., 2009). Thus, the literature demonstrates that the presence of diabetes reduces the ameliorative effect of pharmacological preconditioning on ischemic tissue. However, more research is required to understand the mechanistic basis of the effect of diabetes on pharmacological conditioning to induce ischemia tolerance.

Antidiabetic therapy and effects of conditioning on ischemia-reperfusion injury

There are multiple therapeutic approaches proposed to lower cardiovascular risk among diabetics. One of the approaches involves pharmacological control of blood glucose levels using drugs such as metformin, sulfonylureas, PPAR-γ agonists (thiazolidinedione), α-glucosidase inhibitors and insulin. Other approaches include antihypertensive drugs including ACE-inhibitors, angiotensin-2 receptor blockers, lifestyle interventions, anti-hyperlipidemic drugs, and anti-platelet agents (International Diabetes Federation, 2012). However, given the widespread prevalence of diabetes and associated increases in cardiovascular diseases worldwide, it is also important to understand the potential interactions between these therapeutic approaches and the promising beneficial effect of conditioning. A clinical study by Cleveland et al. evaluated the effect of long-term exposure to oral anti-hyperglycemic agents vs. insulin therapy on ischemic preconditioning in protecting isolated myocardium (right atrial trabeculae) against

ischemic damage (Cleveland et al., 1997). They observed that ischemic preconditioning was able to induce greater recovery of developed force in myocardium from control and in diabetic patients receiving long-term insulin treatment. However, ischemic preconditioning was not able to induce recovery of developed force in myocardium from diabetic patients receiving long-term oral hypoglycemic agents. Glibenclamide and glimepiride are sulfonylurea drugs used for the treatment of T2D (Langtry and Balfour, 1998; Korytkowski et al., 2002). The mechanism of action of their anti-diabetic effects involves inhibition of K_{ATP} channels in pancreatic β-cells (Kramer et al., 1995; Ueda et al., 1999), which are key regulators of insulin release via enhanced intracellular calcium influx (Miki et al., 1998). Glibenclamide attenuates ischemic preconditioning in various laboratory models (Schulz et al., 1994; Miura et al., 1995; Hoag et al., 1997) as well as in human subjects during brief repeated coronary occlusions (in terms of ST segment shift and pain severity) (Tomai et al., 1994). In addition, glibenclamide also attenuates the exercise-induced beneficial effect of the warm–up phenomenon in diabetic subjects (Ovunc, 2000). A double-blind placebo-controlled clinical study showed that while glibenclamide attenuates preconditioning, glimepiride, another K_{ATP} channel inhibitor, maintains the effects of preconditioning in myocardium (Klepzig et al., 1999). It is plausible that glibenclamide and glimepiride may affect other pathways of ischemia tolerance differently, which may explain their differential effects on ischemia tolerance in myocardium.

Metformin belongs to the biguanide category of orally administered anti-diabetic drugs and is the first-line drug for the treatment of T2D (Inzucchi et al., 2012). It acts by reducing "hepatic glucose output" and "increasing insulin-mediated glucose disposal" (Bailey and Turner, 1996), and is one of the most widely used drugs for treatment of T2D (Inzucchi et al., 2012). Metformin, when administered at the time of reperfusion, reduces myocardial infarct size in both the non-diabetic (Wistar rats) and diabetic (Goto-Kakizaki rats) heart, possibly via activation of phosphoinositide 3-kinase, and is associated with Akt phosphorylation (Bhamra et al., 2008). In addition, metformin administration before ischemia or at the time of reperfusion decreases myocardial injury in both nondiabetic and diabetic mice (db/db) (Calvert et al., 2008). Pretreatment with metformin 24 hours prior to permanent middle cerebral artery occlusion reduces infarct size, neurological deficits, and cell apoptosis in ischemic brain (Jiang et al., 2014). Continuous treatment with metformin daily for a period of 3 weeks induces ischemia tolerance resulting in reduced focal cerebral ischemia-induced infarct and neurological deficits, potentially by suppressing NF-κB-mediated inflammatory pathways (Zhu et al., 2015).

There are many new and established anti-diabetic drugs tested for their effect on ischemia tolerance in diabetic animals. 5-hydroxydecanoate, a K_{ATP} channel inhibitor, abrogates the beneficial effect of heat stress preconditioning on heart (Hoag et al., 1997). Repaglinide is reported to attenuate protective effects of myocardial preconditioning in T2D subjects (Rahmi et al., 2013). A study aimed to determine the effect of various pharmacological preconditioning agents on myocardial ischemia using human diabetic myocardium observed that phenylephrine, adenosine, or diazoxide failed to protect diabetic myocardium. In contrast, phorbol-12-myristate-13-acetate (protein kinase C activator), or anisomycin (p38 mitogen-activated protein kinase activator) induced a significant ischemia tolerance in diabetic myocardium (Hassouna et al., 2006). WY-14643, a peroxisome proliferator-activated receptor-alpha agonist, exerts a significant cardioprotective effect on ischemic myocardium in control and Goto-Kakizaki rats, possibly via the activation of phosphoinositide 3-kinase/Akt and nitric oxide pathways (Bulhak et al., 2009). Similarly, rosiglitazone treatment in Zucker diabetic fatty rats exerted a marked cardioprotective effect on myocardium subjected to ischemia (Yue et al., 2005). These studies suggest that the effect of diabetes on ischemia tolerance may vary depending on which glucose-lowering therapy is given. This mixed effect of anti-diabetic drugs on ischemia-reperfusion injury during diabetes also identifies a need for more research in this area.

Future Directions

Overall, the studies discussed in this article clearly demonstrate that diabetes as a comorbid condition affects the beneficial effect of conditioning on ischemic injury. However, studies ascertaining the potential effect of chronic diabetes on the protection afforded by conditioning on ischemic injury in organs like brain, kidney, liver, skeletal muscles and intestines are broadly missing. Given the number of metabolic pathways altered during diabetes and variability in the animal models used to study the effect of diabetes on conditioning, confirmatory studies determining the effect of diabetes on the ameliorative potential of different forms of conditioning would help better characterize the effect of diabetes on the induction of ischemia tolerance. In addition, studies aimed at better understanding the mechanisms by which diabetes affects the beneficial effect of conditioning are also needed. It is also important to evaluate the protective effect of conditioning in treated diabetes. Furthermore, most of the available studies have evaluated the effect of diabetes on ischemia tolerance in young animals. The Centers for Disease Control and Prevention estimates that the prevalence of diabetes is more than 25% in those aged 65 years or older (Centers for Disease Control and Prevention, 2017). The risk of mortality and morbidity due to cardiovascular diseases greatly increases with advancing age in diabetic subjects, as reviewed previously (Cigolle et al., 2009; Kirkman et al., 2012). Therefore, it is important to evaluate the effect of diabetes on conditioning in aged animals. The Stroke Therapy Academic Industry Roundtable (STAIR) research recommendations highlight the clinical significance of studying the effect of comorbid conditions like diabetes on ischemic injury in brain. Application of STAIR criteria for assessing the effect of different forms of conditioning on ischemic tissue would help increase translational potential of various ischemia tolerance induction paradigms.

Summary

Most of the studies aimed at understanding the effect of diabetes on different forms of conditioning demonstrate that diabetes attenuates the effects of various conditioning paradigms, potentially via affecting ischemic tolerance induction pathways. Detailed characterization of mechanisms behind diabetic attenuation of conditioning may help better tailor various conditioning paradigms to induce ischemia tolerance in diabetic patients.

Acknowledgements

This study was supported by National Institutes of Health grant NS073779. We would like to thank Dr. Brant Watson for critical reading of this manuscript.

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